Response to Objection to Information Disclosure Statement

Applicant hereby transmits copies of items listed on his Information Disclosure Statement indicated missing by the Examiner. These items are AE, AF, AH, AJ, AK and AL. A PTO form 1449 listing the references is also submitted herewith.

Request for Reconsideration of Restriction Requirement

Reconsideration of the latest restriction requirement is requested as it relates to the grouping of pharmaceutical compositions of the peptides SEQ ID NO: 9 and SEQ ID NO: 10. Clearly, pharmaceutical compositions containing the SEQ ID NOS: 9 and 10 peptides (claims 6 and 7) are properly grouped within Group I.

Examiner alleges that "the MPEP states that restriction is proper if the inventions are distinct and independent, which means that the sequences although they have some similarities are distinct." Examiner alleges that "any change in residues within the sequence provides a structural difference, hence arguable, a separate protein with a different function". There is no basis in the MPEP for equating separateness and distinctness with differences in amino acid sequences, while ignoring similarities. Examiner's assertion would find separateness and distinctness as between two amino acid sequences which differed in *any* regard, notwithstanding segments of sequence identity. Examiner's logic would prohibit the grouping of peptides that differed by even a single amino acid position. Taken to its logical conclusion, Examiner's position requires that no two amino acid sequences could ever be examined in the same patent application. This is not the law.

Claim 1 defines a genus of pharmaceutical compositions comprising compounds which share the common "core" sequence SEQ ID NO:1. The peptides SEQ ID NO: 9 (grouped by Examiner in Group III) and SEQ ID NO: 10 (not grouped by Examiner in any pharmaceutical composition grouping) contain SEQ ID NO:1 and are therefor properly species of the generic invention of claim 1.

As to SEQ ID NO: 10, contrary to applicant's contention that SEQ ID NO: 10 was ungrouped, Examiner maintains that SEQ ID NO: 10 was grouped into Group V. However, Group V contains claims to methods and not claims to pharmaceutical compositions. Examiner

is respectfully requested to place the pharmaceutical composition of SEQ ID NO: 10 into Group I. The same request is also respectfully made for a pharmaceutical composition of SEQ ID NO: 9 (instead of Group III).

The relationship between SEQ ID NO:1 on the one hand and SEQ ID NOS. 9 and 10 on the other hand is apparent from the following, where the "core" sequence which is SEQ ID NO:1 is indicated in bold:

Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys (SQ1)

Thr-Leu-Thr-His-Thr-Ile-Thr-Lys-Leu-Asn-Ala-Glu-**Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys** (SQ9)

Asn-Asn-Ala-Thr-Phe-Tyr-Phe-Lys-Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg-Val-Glu-Val-Val (SQ10)

SEQ ID NO:9 is composed of the sequence of SEQ ID NO:1, plus an N-terminal segment consisting of the sequence Thr-Leu-Thr-His-Thr-Ile-Thr-Lys-Leu-Asn-Ala-Glu. Similarly, SEQ ID NO: 10 is composed of the sequence of SEQ ID NO:1, plus a C-terminal segment consisting of the sequence Ile-Asp-Asn-Val-Lys-Lys-Ala-Arg-Val-Glu-Val-Val.

The Examiner has provided no factual or legal justification for requiring restriction between SEQ ID NO: 9 (currently in Group III) and the Group I claims. Similarly, Examiner has provided no factual or legal justification for requiring a restriction between SEQ ID NO: 10 (currently not grouped into any composition group) and the Group I claims.

At this point applicant wishes to call the Examiner's attention to the fact that SEQ ID NO: 12 is not classified into any of Groups I – VII. This sequence (see claim 19) is a species of the compound claimed in claim 15 when X_5 and X_6 = 0 amino acids and X_7=Ala. Therefore, SEQ ID NO: 12 should be grouped within Group III.

Also, applicant respectfully seeks clarification as to the underlying rationale for the listing of, for example, claims 8, 12-24 and 46-48 in Group I where, according to the Examiner, Group I is based on SEQ ID NO: 1-4. As to claim 8, 12-21, 23 and 46-48, these are not based on the core sequences of SEQ ID NO: 1-4 but are based on SEQ ID NO: 5, 11, 22, respectively.

Reconsideration of the restriction requirement is respectfully requested, notwithstanding the finality of that requirement.

Response to Section 112, 2nd Paragraph Rejection

Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph. According to the Examiner, claims 6 and 7 are indefinite because they recite non-elected subject matter. These claims are directed to compositions containing the SEQ ID NOS: 9 and 10 peptides, respectively. For the reasons stated above, it is respectfully submitted that claims directed to compositions containing the SEQ ID NOS: 9 and 10 peptides are properly grouped within Group I. The SEQ ID NOS: 9 and 10 peptides contain the common "core" sequence of SEQ ID NO:1, and are therefore properly species of the generic invention of claim 1.

Claim 24, a dependent claim, is rejected as indefinite for the sole reason that it depends from a rejected base claim. Dependence upon a rejected base claim is insufficient grounds to rejection a claim as indefinite.

Response to Section 112, 1st Paragraph Rejection

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph. According to the Examiner, the claims are enabled for the compositions comprising SEQ ID NOS: 1-4, but are not enabled for any fragment thereof. The Examiner incorrectly characterizes the invention as "a composition comprising SEQ ID NOS:1-4 and fragments thereof".

Claims 1, 2 and 3

Claims 1 and 2 do not define the invention on the basis of any "fragments". Claim 1 defines the peptide of the claimed composition as having the "core" sequence SEQ ID NO:1, a flanking N-terminal sequence X_1 of zero to twelve amino acids, and a flanking C-terminal sequence X_2 of zero to twelve amino acids. In claim 2, X_1 and X_2 are from zero to six amino acids. Claim 3, the only claim to utilize "fragment" terminology, is directed to compositions wherein X_1 is the segment SEQ ID NO:1, or N-terminal truncation fragment thereof containing at least one amino acid. X_2 is the segment SEQ ID NO:3, or C-terminal truncation fragment thereof containing at least one amino acid. Thus, the claimed invention is not SEQ ID NOS:1-4 and fragments thereof, and the Examiner has mischaracterized the invention.

To the extent the Section 112 is based upon an interpretation of the claimed invention as a composition of SEQ ID NOS:1-4 and "fragments thereof", the rejection is unfounded because it is not directed to the invention as defined in the claims. Notwithstanding, applicant will endeavor to respond to the rejection as best he can.

In making an enablement rejection, the Examiner has the initial burden of providing a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). "(I)t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id* at 370.

Applicants are not required to provide a working example for every embodiment embraced by the claims. A disclosure which contains representative examples which provide reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim will possess the alleged utility is all that is required, when there is no reason to suspect the assertions are not accurate. *In re Barr*, 170 USPQ 330, 338 (CCPA 1971). The test for enablement is whether one of ordinary skill in the art could make and use the claimed invention, without, undue experimentation, based upon the disclosure in the patent application coupled with information known in the art at the time the patent application was filed. *U.S. Telectronics Inc.*, 8 USPQ2d (Fed. Cir. 1998). Enablement is not precluded even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

Applicant respectfully submits that the specification as filed teaches one of ordinary skill in the art how to make and use the claimed composition without undue experimentation.

Applicant's specification teaches that peptides comprising the SEQ ID NO:1 core sequence inhibit endothelial cell proliferation, and thus possess anti-angiogenic activity. Contrary to Examiner's assertion that no peptide is associated with a disease or bioassay, the specification exemplifies the activity of two such peptides, SEQ ID NO:9 and SEQ ID NO:10, in an assay for endothelial proliferation. The same assay may be used to characterize the activity of

additional peptides containing the core SEQ ID NO:1 sequence. In view of these teachings, a skilled artisan having the benefit of Applicant's teachings, would need to exercise only routine experimentation to practice the claimed invention.

The Examiner has not provided a reasoned explanation for why the skilled artisan would doubt the truth or accuracy of Applicant's disclosure that peptides containing the SEQ ID NO:1 core sequence and up to twelve amino acid N-terminal and C-terminal flanking sequences inhibit endothelial cell proliferation and angiogenesis. The Examiner has not explained why anything more than routine experimentation would be needed for the skilled artisan to practice the claimed invention.

The factors noted by Examiner were no doubt also considered by the PTO in the issuance of Patent 6,284,726 BI (copy enclosed). The subject matter is similar to the subject matter of the present application in that it utilizes peptides from high molecular weight kininogen to inhibit angiogenesis, but differs in that the peptides are selected from kininogen domain 5, not domain 3. The '726 patent's claim 12, which is similar in structure and even greater in scope than the instant claim 1, issued based upon a characterization of activity of just three peptides - SEQ ID NOS:5, 9 and 10. See Example 1, col. 10 -11.[1] Contrary to Examiner's assertions, the issuance of the '726 patent establishes that one of ordinary skill in the art would indeed be able to practice the invention as claimed in the instant application without undue experimentation.

The '726 patent, claim 12, is directed to a pharmaceutical composition comprising a peptide, wherein the peptide is defined by:

> a "core" segment consisting of the fifteen HK amino acids His(441) to His(455) (col. 2, lines 47-49);
>
> an N-terminal flanking sequence, X_1, consisting of zero to 25 amino acids;
>
> a C-terminal flanking sequence, X_2, consisting of zero to 45 amino acids;
>
> wherein the flanking sequences may be comprised of *any* amino acids.

[1] Of the six tested peptides in the '726 patent, only SEQ ID NOS:5, 9 and 10 were within the scope of claim 12.

The instant claim 1 is directed to a pharmaceutical composition comprising a peptide, wherein the peptide is defined by:

> a "core" segment consisting of the nine HK amino acids Asn(275) to Lys(282);
> an N-terminal flanking sequence, X_1, consisting of zero to 12 amino acids;
> a C-terminal flanking sequence, X_2, consisting of zero to 12 amino acids;
> wherein the flanking sequences may be comprised of any amino acids.

Claim 12 of the '726 patent is principally supported by a showing that the peptides SEQ ID NOS:5, 9 and 10 inhibit proliferation of human umbilical cord vein cells (HUVEC), a type of endothelial cell. See Table 1, col. 11. Instant claim 1, which is in the same format but has a narrower scope than '726 patent claim 12, is similarly supported by the anti-proliferative activity of two peptides shown to inhibit HUVEC proliferation: SEQ ID NO:9 and SEQ ID NO:10 (Table 1, page 24).

The issuance of the '726 patent demonstrates that one of ordinary skill in the art would be deemed able to practice the instantly claimed invention without undue experimentation, due to the similarity of subject matter, claim structure and supporting disclosure between the present application and the '726 patent.

Turning to certain specifics of the rejection, Examiner asserts that the following elements of claim 3 are somehow improper because they omit a "functional limitation as to use of the claimed composition":

> "the segment SEQ ID NO:2, or N-terminal truncation fragment thereof containing at least one amino acid" and
>
> "the segment SEQ ID NO:3, or C-terminal truncation fragment thereof containing at least one amino acid"

In the absence of "functional language", Examiner alleges one skilled in the art would have to engage in undue experimentation to determine if the "fragment" has the activity set forth in the disclosure. Examiner further alleges that the working examples do not demonstrate "the claimed fragment in association with the claimed invention".

Examiner has misconstrued claim 3. The peptide defined in claim 3 comprises the core sequence of SEQ ID NO:1 flanked by (i) SEQ ID NO:2, or N-terminal truncation fragment of SEQ ID NO:2 containing at least one amino acid and (ii) SEQ ID NO:3, or C-terminal truncation fragment of SEQ ID NO:3 containing at least one amino acid. The "fragment" of SEQ ID NO:2 and the "fragment" of SEQ ID NO:3 which may be contained in the claimed peptide need not own their own display biological activity. Rather, it is the association of such flanking segments with the core sequence SEQ ID NO:1 which gives rise to an anti-angiogenic of the entire peptide.[2] Thus, Examiner's requirement of a "functional limitation" coupled to the "fragment" element of claim 3 is misplaced, as those fragments in and of themselves are not expected to be active. The same is thus also true of Examiner's challenge that the specification "does not provide a definition or any details regarding the characteristics of the claimed fragment" or "does not exemplify the claimed fragment in associate with a disease of in a bioassay". The "fragments" of SEQ ID NO:2 and SEQ ID NO:3 are not the active peptide defined in claim 3, but only a part of the active peptide.

Even assuming *arguendo* that Examiner's comments aimed at "fragments" may be interpreted as applying to the *peptides* as they are in fact claimed by applicant, the rejection is contrary to PTO precedent. With respect to the compositions defined by claims 1, 2 and 3, claims of virtually *identical* claim format for defining anti-angiogenic peptides were allowed by the Office in the '726 patent. See claims 12, 13 and 14 of the '726 patent. The Office granted such claims without any functional limitation in the claims for the use of the claimed composition. The Office granted such claims with the same level of supporting detail in the specification regarding the characteristics or properties of the claimed peptides. Moreover, contrary to the assertion of the lack of a working example and a bioassay, peptides of the present invention (SEQ ID NO:9 and SEQ ID NO:10) were indeed shown to inhibit proliferation of HUVEC, just as in the '726 patent. Inhibition of HUVEC proliferation demonstrates that the

[2] In one sense, the peptides of claim 3 may be considered "fragments" of HK. The largest peptide of claim 3 is represented by the linear combination of SEQ ID NO:2-SEQ ID NO:1-SEQ ID NO:3. This corresponds to the native HK sequence consisting of HK amino acids Thr(263) to Val(294). The peptides of claim 3 may thus be viewed as "fragments" of HK domain 3, which fragments contain the required core sequence SEQ ID NO: .

peptides are useful for inhibiting conditions, such as angiogenesis, which are characterized by endothelial cell proliferation.

Again mischaracterizing the peptides of the invention as *fragments*, the rejection maintains that the specification lacks "guidance/direction as to the attributes of the claimed fragment, i.e., size, structure and function". Examiner asserts that "no guidance is provided as to which one or more amino acids are removed from the terminals and in what positions." and that the working examples "do not demonstrate the claimed fragments in association with the claimed invention". Assuming Examiner's remarks with respect to "*fragments*" are directed to claim 3 (the only claim which refers to "fragments"), those remarks are inappropriate because the fragments referenced therein are not the entire peptide defined therein (X_1-SEQ ID NO:1-X_2), but only serve to limit the scope of the flanking sequences X_1 and X_2. The specific "guidance/direction" is that the "core" sequence of SEQ ID NO:1 must be preserved, and that the flanking sequences X_1 and X_2 may be varied. In fact, the same quantum of "guidance" is given in the '627 patent for claim 14 thereof, a claim which is cast in a format identical to the instant claim 3.

With regard to the alleged unpredictability of the art, the same considerations applied to the subject matter of the '627 patent. Yet claims were granted in the '627 patent to anti-angiogenic HK-based peptide compositions of even broader scope than the instant claims with the same degree of specification support, thus demonstrating that the alleged unpredictability of the art is not a barrier to claims of the scope presented herein.

It is respectfully submitted that claims 1, 2 and 3 are adequately supported by the disclosure.

Claim 4 is directed to compositions wherein the included peptide has substantial amino acid sequence homology to SEQ ID NO:1. Substantial homology is defined in the specification, page 13, as at least 30% homology. No basis is given in the office action for rejection of this claim under Section 112.

Claims 5, 6 and 7 are directed to compositions of peptides having stated amino acid sequences. The rejection of these claims for lack of enabling disclosure on the rational advance

by Examiner is incorrect, since the scope of peptide embraced by each of these claims is a single peptide.

In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

In conclusion, applicant respectfully submits that the claims remaining in the application are in condition for allowance. An early notice of allowance is earnestly solicited.

Respectfully submitted,

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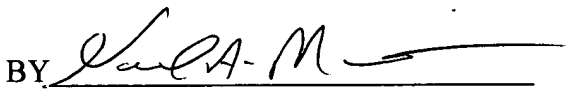
BY 

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